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Prototype Model of Human Feeding, Growth and Obesity

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I. Presuppositions

A. *Tentativeness of the Approach*

Some recent experimental results (Booth, 1977a; Booth *et al.*, 1976b) suggest that the outlines of the biological and learned bases of hunger in man are similar to those already elucidated in somewhat more detail in the rat. This should not be too surprising in so far as the rat is similar to man in being an omnivore species and possessing the basic mammalian equipment viscerally and cerebrally that is more elaborate in us. Indeed, not just because we already know a good deal about the rat, but purely on homocentric grounds, the physiology and learning mechanisms involved in appetite in the intact rat, particularly when fed on a variety of diets, should be considered worthy of intensive study.

Despite this, and despite the relative success of our systems analysis of feeding control in the rat (Chapter 11), we had considerable reservations about attempting to extend such modelling to man. In the first place, although functions and parameter values for human beings could be roughly specified, precise relevant data were even more sparse than in the rat. As in the animal laboratory, over-restrictive notions of scientific rigour have dominated the design of experiments. The traditions of human physiological experimentation have until very recently failed to provide us with good measurements in subjects taking their normal diet on a normal schedule during a normal day's work, and the role of learning in normal feeding has hardly been a topic of experimentation at all. Secondly, social determinants would presumably be dominant in the human case, however great the importance of the biological substructure of

human appetite and learned accommodations to it. A simulation not taking account of social influences on feeding might therefore be most unrealistic in its predictions.

Nevertheless, an attempt to build a human version of our systems analysis of feeding should at least expose the limitations of an approach with a focus restricted to biological determinants of human appetite and so point to new lines of experimental or clinical investigation. At best, it could pave the way for a theoretically well founded and clinically useful model of a realistic combination of biological, cognitive and social controls.

B. *General Theory: The Energy Flow Cycle*

We assumed that appetite is the expression of an incipient deficiency in the net supply of energy to working tissues, in behavioural tendencies or attitudes which favour means of correcting that deficiency. Satiation, i.e. loss of appetite during feeding, is an anticipation of what would without a change in behaviour be an over-correction of the deficiency. The sensations that an individual habitually experiences either when he has an appetite or when he has satisfied it are identifiable subjective correlates of a potentially low or high energy supply. Motivation to eat food results from effects on cerebral activity of states of the stomach, intestines and body tissues which reflect their content or net input of metabolizable energy.

Knowledge about the body and the effects of food on it could be based on initially undifferentiated distress states of gross energy deficiency or excess. Unlearned reaction patterns could ensure feeding occurs during nursing, when control may not be needed. The characteristics and relevance of bodily sensations or particular foodstuffs could then be progressively discriminated during infancy and childhood by means of natural experience of feeding in relation to need. The pleasantness of a foodstuff is assumed to be at least in part an anticipation of the effects of ingesting it on the supply of energy to critical tissues.

It would of course be extremely difficult to specify every physiological or cognitive detail of energy-related information possessed by an individual from one moment to the next. However, such detail might not be needed in order to calculate the relation of behaviour to energy need. The particular flavours that rich foods have in a given culture, the precise physical or chemical effect of a meal in the gut or the tissues which serves as a satiety signal, or the speed or other characteristics of learning—this might all be information which is redundant for the purpose of generating some major predictions of feeding behaviour, and its consequences for body compositon.

The energy requirement is not of course the only need met by feeding. It is

however by far the largest nutrient requirement apart from water, particularly if each essential amino acid is considered separately. Furthermore, when no extreme ecological, cultural or economic constraints are operative, mixed diets supply adequate amounts and balances of amino acids, salts, fatty acids and vitamins if the dietary mixture is taken in a calorically sufficient quantity. Thus, normal hunger may be purely an energy appetite. Even if in fact other specific appetites can and do operate, they may only be influential in unusual conditions or in the fine details of foodstuff selection. A representation for acquired protein appetite could in due course be included in a model of human feeding, if it proves to be more realistic to complement energy-specific appetite in that way.

A detailed development of this view of hunger has been put into one of many possible specific forms or models suitable to be programmed for computer simulation.

II. A Computer Program for a Basic Model

A model is typically represented by a family of related computer programs. Each particular program may be used for a variety of simulation runs: values of some parameters in the model can be changed from run to run to simulate different conditions in the real system. To help in exposition of the workings of our prototype model of human feeding control, a stripped-down version has been constructed. Statements which comprise a program for this basic model are listed in Figs 1–6. The remainder of this section is an explanation which does not require knowledge either of programming or of the details of the theory of hunger on which the model is based. Some readers may be interested to see the exact computational procedures in this case, particularly as a working computer program is not given in any other chapter in this book.

A. *Starting Data*

1. *Computational Declarations*

(a) *Arrays*. The program uses two one-dimensional tabulations during the calculations. One stores a continuously updated list of what is roughly speaking the contents of the successive portions of a notionally segmented small intestine (GUTLAG). The other lists the fraction of work output to be added to basal metabolic rate as activity varies around the clock (FMETAB). These dimensions have to be declared at the beginning of a program list (statement 1, Fig. 1).

(b) *Real and integer variables*. The programming language Fortran treats variables which are meant always to be whole numbers (INTEGER) differently from variables whose values are always to be regarded as going to at least one decimal place (REAL). The characteristics of each variable have to be declared

```
      C COMPUTATIONAL DECLARATIONS
0001        DIMENSION GUTLAG(20), FMETAB(3000)
0002        REAL MAXFLO, LIPO, MINFLO, INFAT, METABR, LEAN, OUTFAT, STOMAK
0003        REAL DENSIT, ERATE, WORK, FATFBK, ACQOFF, WEIGHT, FAT
0004        REAL T2, T3, T4, T5, HUNGER, CONT, ABSOR, PERIOD, STOP, FMETAB(3000)
0005        REAL T1, GUTLAG(20), FLO, START, SINCE
0006        REAL DAYFAT, DYLEAN, ACON, AFA, ALEA, FATDAY, LEANDY
0007        INTEGER SECOND, DAY, DAYS, MINUTE, HOUR, CYCLE, DIGEST, D1GEST, COUNT
0008        INTEGER N, NEND, MMI, MSIZE
```

Fig. 1. Initial declarations of dimensions and numerical types of variables. This is the first part of a program list written in Fortran for a basic version of the prototype human feeding model. The rest of the program is given in Figs 2–6. Lines beginning "c" are comments not used by the computer. The statement numbers on the far left are also not part of the program proper.

at the start of the program (statements 2–8, Fig. 1). The meanings of all the variables are explained below.

2. *Values of Parameters and Variables*

The simulation requires boundary and initial conditions to be set and also values for the various parameters in the mathematical functions to be used in the calculations. In interactive versions of the model, the program can be written so that the computer asks the user to choose a value in the case of any values that are frequently varied from one simulation to the next. Such preliminary questions are not included in this program but the structure of variables underlying them is maintained for clarity of exposition.

(a) *Body composition.* The weight of the person being simulated is stated in kilograms (statement 9, Fig. 2). As WEIGHT is a real variable (statement 3, Fig. 1), it must be stated to at least one decimal place even if the value is in fact an integer. Adipose tissue is taken to comprise 15% of body mass in this instance, and in effect all fat is supposed to reside in adipose. The energy density of

```
      C VALUES OF PARAMETERS AND VARIABLES
0009        WEIGHT=75.0
0010        FAT=WEIGHT*15.0*7700.0/100.0
0011        LEAN=WEIGHT*85.0*3000.0/100.0
0012        WORK=1.4
0013        T2=900.0
0014        T3=1080.0
0015        T4=2040.0
0016        T5=2820.0
0017        NEND=2880
0018        DENSIT=1.9
0019        ERATE=25.0
0020        STOMAK=.193
0021        DIGEST=12
0022        INFAT=.56
0023        OUTFAT=.43
0024        FATFBK=-1.0E-06
0025        MINFLO=-1.07
0026        MAXFLO=1.46
0027        ACQOFF=1.08
0028        STOP=0.0

      C INITIAL CONDITIONS
0029        HUNGER=0.0
0030        CONT=0.0
0031        ABSOR=0.0
0032        SECOND=0
0033        MINUTE=0
0034        HOUR=0
0035        DAY=-1
0036        DAYS=3
0037        N=0

      C CALCULATION PARAMETERS
0038        CYCLE=30
0039        PERIOD=0.5
0040        COUNT=DIGEST+1
0041        D1GEST=DIGEST+1
0042        FATDAY=FAT
0043        LEANDY=LEAN
```

Fig. 2. Setting parameters to their standard values, variables to their initial values, and fixing calculation parameters.

adipose is taken to be 7·7 Mcal/kg. Thus statement 10 (Fig. 2) calculates the fat energy of the body in kilocalories. The remaining mass is designated lean, and its energy content is calculated from an average density of 3 Mcal/kg (statement 11).

(b) *Daily activity pattern.* This version of the model includes a very crude specification of the variation in energy loss around the clock. The energy costs of posture, movement and external work are supposed to run at a constant maximum for the working period of the day, and are assumed to be zero during sleeping hours. In this particular instance, very low activity costs of 1·4 kcal/min are specified (statement 12, Fig 2). Statements 13–17 specify times of waking, starting full work, stopping work, and going to sleep, respectively, ending with the time at which the 24-h period ends. The time unit here is 30 sec, because this is the time base on which all the calculations are done in this version: there are 2880 half-minutes in 24 h (statement 17). Waking is at 900 half-minutes, i.e. 7.30 a.m. (statement 13), and so on.

(c) *Alimentary parameters.* The energy density of the diet is taken to be 1·9 kcal/g (statement 18, Fig. 2). This version of the model does not distinguish component foodstuffs within the diet. Eating rate is also taken to be a constant, namely 25 g/min (statement 19). Both these parameters could easily be programmed to vary independently during meals, e.g. water content affecting density, and textures or flavours affecting eating rate. In this basic version there is probably little point, as we believe that learning processes not represented in it (see Section VI.A) would be important in calculating the effects of major variations of that sort. In fact, this program needs only an energy rate of ingestion, which could have been specified in a single statement.

The major determinant of the rate of energy flow to the body is the rate of gastric emptying. This is calculated in kcal/min from the amount of food energy (kcal) in the stomach, according to the equation in statement 55 (Fig. 4). STOMAK (statement 20) is the proportionality factor in this gastric emptying function. The larger that this parameter STOMAK is, the higher the rate at which the stomach pumps out nutrient for a given amount in the stomach.

It may be noted that this and the following six parameters hae been adjusted to provide approximately stable body composition (see Section IV.A.1 and B).

Digestion, and to a lesser extent transit between the mouth and stomach and between intestinal lumen and tissues, take a significant time compared with the duration of a meal. In this prototype model, these delays are represented simply as a lag (DIGEST) between gastric clearance and the energy reaching the hunger/satiety receptor system which transduces net energy flow to lean tissues into neural activity controlling feeding onset and offset. In a more advanced model it might be possible to simulate the molecular and cellular processes of

digestion and replace a simple delay by more realistic functions. DIGEST (statement 21) is here set equal to 6 min.

(d) *Fat deposition and mobilization.* The flow of energy into or out of fat is calculated on the simplifying assumptions (discussed later in the chapter, Section IV.C.2) that net lipogenesis occurs in proportion to the excess of energy supply over energy consumption and that net lipolysis is in porportion to deficit of supply relative to consumption. The proportionality factors INFAT and OUTFAT (statements 22 and 23, Fig. 2) are assumed to differ.

A small continuous addition to lipolysis is assumed to arise from a basal level of fat mobilization in proportion to total fat energy. FATFBK (statement 24) is the proportionality factor in the equation (statement 70, Fig. 4) used to calculate this negative feedback signal from fat store size into the satiating energy flow. FATFBK is negative because it is a loss of energy from total fat. It is a very small number because it translates tens of thousands of kilocalories of fat store energy into a fraction of a kcal/min of fat mobilization. In statement 24, "E-06" means an exponent or power of minus six, i.e. FATFBK $= -1 \times 10^{-6}$.

(e) *Hunger and satiety thresholds in this basic version of the model.* The onset and offset of feeding is determined directly by particular values of the rate of flow of energy into non-fat components of the body. Feeding starts when this energy flow goes below the value of the parameter MINFLO (statement 25, Fig. 2). Feeding ends when energy flow goes above a satiety threshold which has been acquired by past experience of the energy flow following the end of a meal. MAXFLO (statement 26) sets a target for the flow maximum which is reached as absorption peaks after the delay for digestion to catch up with the rate of gastric emptying. The acquired satiety threshold ACQOFF is adjusted up or down after a meal to approximate the next postprandial peak to the target value (statement 99, Fig. 5). In statement 26, ACQOFF is given a starting value which approximates to the value it would acquire for the second meal: this removes the possibility that first simulated meal would be very abnormal and the simulation would take longer to stabilize. Of course, if just such a transient were of interest, ACQOFF could be made equal to MAXFLO, or given any other relevant starting value.

STOP (statement 28) is a tag which is used to calculate meal sizes (statements 81 and 89–90, Fig. 5). It must be set to zero for the start of the simulation.

3. *Initial Conditions*

A number of tags and variables have to be declared before they are invoked during calculations, and have to be given some value. The very first cycle of calculation would rectify any anomalies in the values given here. HUNGER (statement 29) is a tag set to unity by the onset of the tendency to feed and reset

to zero by the offset of feeding. Stomach contents (CONT) and the rate of intestinal absorption (ABSOR) are set to zero initially. This is consistent with zero hunger, because the simulation is started at midnight (statements 32–34) when the person is asleep and there is no tendency to feed even if the gut is empty. The number of the day before the start (DAY) and the number of days after which the simulation is to stop (DAYS) are set to give three days of output (statements 35 and 36). Statement 37 sets to zero (midnight) the count which is increased by one at each iteration of the calculation cycle (see statement 100, Fig. 6), until another 24 h has elasped (statements 108 and 109).

4. *Calculation Parameters*

Finally, some computational "housekeeping" has to be done before the simulation proper can begin.

(a) *Calculation cycle.* The model works on the principle of calculating a new state of every variable at a fixed interval of simulated time after the last calculated state. This procedure of successive addition makes the mathematical operations in the program much easier to understand for those of us to whom differential equations are something of a mystery. Furthermore, it bypasses difficulties which may arise in constructing or using the appropriate continuous mathematics. If the time interval between the calculated states is short enough relative to the rates of changes in states within the real system, successive addition will give results not appreciably different from integration.

There are changes every few seconds in the physiological and psychological processes which are critical at the level of systems analysis on which this model is operating. However, the changes are probably slow enough to be approximately constant in rate for a quarter or half a minute at least. We have generally run simulations of human feeding on a calculation cycle of 30 seconds or less. When the basic model given here is run on calculation cycles of 10 seconds or less the results are very similar. The duration of the time step is specified in seconds (CYCLE, statement 38) and minutes (PERIOD, statement 39). COUNT and DIGEST (statements 40 and 41) are tags used to detect the postprandial energy flow maximum (statements 95–99, Fig. 5) which is simply the energy flow value after the digestion lag DIGEST. Midnight values of fat and lean energy (FATDAY and LEANDY) are given the starting values of these body energy components (statements 42 and 43).

Statements 44–50 (Fig. 3) fill the FMETAB array with a list of values of the activity component of metabolic rate corresponding to each half-minute around the clock (= 2800 calculation cycles). Between waking and the start of the working period these values are fractions linearly increasing from zero to full working rate (statement 47). They are linearly decreasing from the end of work until bedtime (statement 49). During the sleep period, zero values are entered in

```
0044          DO 100 I=1,2880
0045          FMETAB(I)=0.0
0046          T1=FLOAT(I)
0047          IF(T1.GT.T2.AND.T1.LT.T3) FMETAB(I)=(T1-T2)/(T3-T2)
0048          IF(T1.GE.T3.AND.T1.LE.T4) FMETAB(I)=1.0
0049          IF(T1.GT.T4.AND.T1.LT.T5) FMETAB(I)=(T5-T1)/(T5-T4)
0050      100 CONTINUE
0051          DO 1 I=1,D1GEST
0052          GUTLAG(I)=ABSOR
0053        1 CONTINUE
0054          GO TO 10
```

Fig. 3. Filling the arrays of the fractional work metabolism pattern and the digesting intestinal contents.

places in the array corresponding to the sleep period. This array could in principle include values which represented any pattern of activity for which it was of interest to test the model.

Statements 51–53 fill the array of intestine contents with zeros, to displace any values which might otherwise be created by the initial state of the computer.

Statement 54 then specifies a jump to the labelled statement 111 (Fig. 6), which sets the day number to zero. This in turn permits statement 112 to be used for the first and last time, leading to statements 120–126 which print the titles of the columns on the output and a dummy line reporting the states of variables (see Fig. 7), before starting the first calculation cycle at the labelled statement 55.

B. *Main Calculations*

The part of the program list concerned primarily with calculating values of energy flow rates is given in Figs 4 and 5.

```
      C          CALCULATION CYCLE

      C STOMACH CONTENTS

0055        2 CONT=CONT+PERIOD*(HUNGER*DENSIT*ERATE-STOMAK*SQRT(CONT))
0056          IF(CONT.LT.0.0)CONT=0.0
0057          ACON=CONT/1000.0

      C INTESTINAL LAG IN ABSORPTION

0058          DO 3 I=2,D1GEST
0059          GUTLAG(I-1)=GUTLAG(I)
0060        3 CONTINUE
0061          GUTLAG(D1GEST)=STOMAK*SQRT(CONT)
0062          ABSOR=GUTLAG(1)

      C METABOLIC RATE

0063          METABR=WEIGHT/60.0+FMETAB(N+1)*WORK+ABSOR*0.05

      C LIPID FLOWS

0064          IF(ABSOR-METABR)101,102,103
0065      101 LIPO=OUTFAT*(ABSOR-METABR)
0066          GO TO 105
0067      102 LIPO=0.0
0068          GO TO 105
0069      103 LIPO=INFAT*(ABSOR-METABR)
0070      105 LIPO=LIPO+FAT*FATFBK
0071          FAT=FAT+PERIOD*LIPO
0072          AFA=FAT/1000.0
```

Fig. 4. Start of the main calculations.

1. *Stomach Contents*

The energy content of the stomach (CONT) is updated by statement 55 (Fig. 4). This adds to the pre-existing gastric contents the amount of energy which might have been eaten since the last calculation cycle (PERIOD min ago) while subtracting what has been cleared from the stomach in that time.

The computational variable HUNGER is set at unity when feeding occurs and at zero when there is no feeding. The energy rate of feeding is the multiple of the diet's energy density (DENSIT) and the weight rate of feeding (ERATE). Thus HUNGER times DENSIT times ERATE is the current energy rate of feeding.

The current rate of energy clearance from the stomach is calculated from the energy content (CONT) remaining from the last calculation cycle. As discussed in Chapter 11, stomach emptying rate is generally close to proportional to the square root of stomach contents. Therefore, the rate of loss of energy from the stomach is the square root ("SQRT") of its contents multiplied by the rate constant specified at the start of the simulation (STOMAK, statement 20, Fig. 2).

The difference between rate of energy loss from the stomach and any energy gain by feeding, expressed in kcal/min, is multiplied by the simulated time since the last calculation in minutes (PERIOD, statement 39, Fig. 2). This gives the net gain or loss of energy which, when added to the original value for stomach energy content, gives the new value.

After the stomach has become practically empty the equation of statement 55 might occasionally give values of CONT very slightly less than zero. This is not merely physically unrealistic; it creates the computational fault of attempting the square root of a negative number at the next use of 55. Therefore statement 56 sets the value for stomach contents exactly to zero immediately if it happens to become negative. Statement 57 merely scales stomach contents to megacalories for output (statements 124 and 128, Fig. 6).

2. *Intestinal Contents and Absorption*

The delay between energy leaving the stomach and reaching tissues after digestion and absorption is handled by storing a series of recent flow values from the stomach in an array. The series is as long as the simple delay representing digestion which was specified before calculation cycles began (DIGEST, statements 21 and 41). Statements 58–61 (Fig. 4) update this array. Each flow value is moved along one step (statements 58–60) and the current rate of energy flow from the stomach is entered in the newly vacated first step in the array (statement 61), using the square-root clearance function as in statement 55. The most ancient stomach clearance rate value, from the other end of the array (at DIGEST +1), is then taken as the current rate of absorption (statement 62).

3. *Metabolic Rate*

Statement 63 (Fig. 4) calculates current metabolic rate in the conventional manner by adding its several components. Basal metabolic rate is calculated from current body weight (WEIGHT) by simple proportion, a reasonable approximation over the range of body weights usually considered during modelling with this prototype. Further energy expenditure is added to allow for posture, movement and external work at times of day when the modelled subject is not in bed: the fractional level of activity for the current half-minute time unit ($N + 1$) is read from the activity pattern listed in the FMETAB array (statements 44 to 50) and multiplied by the full working rate of expenditure (WORK, statement 12). Finally, the energy lost in processing food (thermic effect, formerly called "specific dynamic action") is added, estimated in this case as 5% of the rate of absorption. Failure to absorb a small fraction of metabolisable energy, and consequent faecal energy loss (plus any insensible and urinary energy losses), should be represented in the most accurate model.

4. *Fat Deposition and Mobilization*

On the assumption that net lipogenesis occurs in proportion to the excess of energy supply over energy consumption and that net lipolysis is in proportion to deficit of supply relative to consumption, metabolic rate is taken to represent the main component of energy consumption. The proportionality factors are assumed to differ between lipogenesis and lipolysis, with a large fraction of any excess being diverted into fat deposition, but a more modest fraction of any deficit being met from lipolysis. Thus, one equation is used during deficit (statement 65, Fig. 4) and another during excess (statement 69). These equations give lipolytic energy flow a negative value and lipogenic flow a positive value. Statement 64 uses a Fortran algorithm to specify which equation is used: which of the three labelled statements listed (101, 102, 103) is used depends on the value of the IF function. If metabolic rate is greater than absorption rate (ABSOR-METABR is negative), 101 is used (statement 65: lipolysis). If the rates are equal, 102 is used (zero lipoflow). If absorption is faster than metabolism, 103 (statement 69: lipogenesis) is used.

If it is supposed that the amount of fat in adipose cells influences their lipogenic or lipolytic characteristics, this coupling of fat store size to current energy flow can also be represented at this stage of the calculations. In this program, statement 70 represents a lipolytic bias which increases with adiposity, as strongly or as weakly as the limited stability of body fat content may imply (see Section V.C.1): the strength of this feedback is set by the proportionality factor FATFBK of statement 24 (Fig. 2).

The fat content of the body is then increased or diminished according to the current flow of energy into or out of fat (statement 71) and adipose energy scaled to megacalories for output (statement 72).

5. *Non-fat Energy Flow and Storage*

The net energy flow to parenteral tissues excluding fat (FLO) is calculated by statement 73 (Fig. 5). Lipogenesis (or the negative flow of lipolysis) and total metabolic rate are subtracted from absorption.

```
      C FLOW INTO AND OUT OF LEAN TISSUE

0073        FLO=ABSOR-LIPO-METABR
0074        LEAN=LEAN+PERIOD*FLO
0075        WEIGHT=LEAN/3000.0+FAT/7700.0
0076        ALEA=LEAN/1000.0

      C MEAL START

0077        IF(HUNGER.GT.0.5) GO TO 5
0078        IF(FLO.GT.MINFLO) GO TO 7
0079        HUNGER=1.0
0080        START=FLOAT(N)
0081        SINCE=(START-STOP)*PERIOD
0082        IF(SINCE.LT.0.0)SINCE=SINCE+1440.0
0083        MMI=IFIX(SINCE)
0084        WRITE(6,4)HOUR,MINUTE,MMI
0085      4 FORMAT(/1H0,12HMEAL STARTED,4X,4HTIME,2I3,
           14X,18HMEAL-MEAL INTERVAL,I5,3X,7HMINUTES)

      C END OF MEAL

0086        IF(HUNGER.LT.0.5) GO TO 7
0087      5 IF(FLO.LT.ACQOFF) GO TO 7
0088        HUNGER=0.0
0089        STOP=FLOAT(N)
0090        SINCE=(STOP-START)*PERIOD
0091        MSIZE=IFIX(SINCE*ERATE)
0092        WRITE(6,6)HOUR,MINUTE,MSIZE,ACQOFF
0093      6 FORMAT(1H ,12HMEAL STOPPED,4X,4HTIME,2I3,
           14X,9HMEAL SIZE,I6,2X,5HGRAMS,11H    OFF USED,F5.2)
0094        COUNT=0

      C CONDITIONING OF SATIETY

0095      7 IF(COUNT-DIGEST)201,202,9
0096    201 COUNT=COUNT+1
0097        GO TO 9
0098    202 COUNT=DIGEST
0099        ACQOFF=ACQOFF-(FLO-MAXFLO)
```

Fig. 5. Decisions to start and to stop feeding.

The last calculated non-fat energy flow rate is used to calculate the latest addition to or loss from non-lipid body energy (statement 74), scaled to megacalories by statement 76. This change in non-fat energy would roughly correspond to growth or wasting of lean body mass. Current fat energy and non-fat energy are both converted from kilocalories to kilograms and added to give current body weight (statement 75), ignoring the weight of current gut contents.

The net postintestinal flow of energy to non-fat mass is assumed to be sampled by the receptor system which controls appetite and its satiation. Thus the value of FLO is critical to the rest of the calculations.

6. *Deciding to Start or to Stop Feeding*

(a) *Meal Start.* Competing motivations and social and other external constraints are not represented in this simplified model. Also the diet is treated as a single unit of fixed availability and palatability. Under such conditions, the decision to start feeding is assumed to be determined entirely by the current supply of energy to lean tissues.

The relevant statements are given in the continuation of the program list in Fig. 5. Unless the system is already feeding (i.e. HUNGER has already been set equal to unity and is greater than 0·5, statement 77), the current energy flow (FLO) is compared with the hunger threshold (MINFLO) (statement 78, Fig. 5). If energy flow is below threshold, then the feeding tag is activated (statement 79) and the meal start-time tag is set at the current time in half-minute calculation cycle units (statement 80).

Statements 81–85 then calculate the interval since the end of the last meal (START minus STOP) and specify a print-out of the time at which the meal has started and of the meal-to-meal interval (MMI).

(b) *Meal finish.* If, on the other hand, the system is already feeding (HUNGER is unity and *not* less than 0·5, statement 86), energy flow is compared with another threshold (statement 87, Fig. 5), and if flow is above threshold the tendency to feed is stopped (the HUNGER tag is zeroed, statement 88) and the time of stopping noted (statement 89). This effective satiety threshold (ACQOFF) has a value which has been established on previous calculation cycles following the occurrence of meals (see next section).

The time from START to STOP (statement 90) gives meal size when multiplied by eating rate (statement 91). Statements 92 and 93 then print out the time of the end of the meal, the meal size and the satiety threshold value used.

7. *Conditioning of Satiety*

A tag (COUNT) counts the number of calculation cycles from the end of a meal (statement 94) until the count corresponds to the length of the digestion lag (DIGEST). Then on that cycle the program no longer skips over a statement which will adjust the satiety threshold (statement 99, Fig. 5). In statement 95 before then, COUNT minus DIGEST is negative and label 201 is followed, merely adding one to COUNT (statement 96). After then, COUNT minus DIGEST is positive and label 9 is followed, skipping the conditioning of satiation threshold and going to statement 100 (Fig. 6).

After the period of the digestion delay following the end of a meal, the peak gastric clearance rate generated by peak gastric contents will have worked through to a peak absorption rate. This in turn will have brought net energy flow (FLO) to a peak. Thus the conditioning adjustment of the satiety threshold by statement 99 only occurs on the calculation cycle when FLO is at its postpran-

dial maximum. The adjustment is to add the difference between the energy flow at maximum (FLO) and standard target maximum energy flow (MAXFLO, statement 26, Fig. 2). The effect of this is that if energy flow overshoots target, the satiety threshold is reduced, tending to produce a smaller meal and a lower maximum at the next meal. On the other hand, if energy flow undershoots, the threshold is raised and the next meal is bigger.

C. *Time Monitoring and Output Routines*

1. *Updating*

The calculation cycle is completed by adding one to the cycle number before starting a new cycle (statement 100, Fig. 6) and updating all components of the

```
      C UPDATE TIME

0100      9 N=N+1
0101        SECOND=SECOND+CYCLE
0102        IF(SECOND.NE.60) GO TO 2
0103        MINUTE=MINUTE+1
0104        SECOND=0
0105        IF(MINUTE.NE.60) GO TO 14
0106        HOUR=HOUR+1
0107        MINUTE=0
0108        IF(N.NE.NEND) GO TO 14
0109        N=0
0110        HOUR=0
0111       10 DAY=DAY+1

      C DAILY CONDITION REPORT

0112          IF(DAY.EQ.0) GO TO 12
0113          DAYFAT=FAT-FATDAY
0114          DYLEAN=LEAN-LEANDY
0115          WRITE(6,11)DAY,DAYFAT,DYLEAN
0116       11 FORMAT(1H0,10X,10HEND OF DAY,I3,3X,3HFAT,F6.1,
                3X,4HLEAN,F6.1)
0117          FATDAY=FAT
0118          LEANDY=LEAN
0119          IF(DAY.EQ.DAYS) STOP

      C PAGE TITLES

0120       12 WRITE(6,13)
0121       13 FORMAT(1H1,' TIME    METABR    GUT    ABSOR   LIPO
             1   FLO     FAT    LEAN   WEIGHT ',/)

      C REPORT DECISION STATEMENTS

0122       14 IF(HUNGER.GT.0.5) GO TO 16
0123          IF(MINUTE.NE.0) GO TO 2

      C ROUTINE HOURLY REPORTS

0124          WRITE(6,15)HOUR,MINUTE,METABR,ACON,ABSOR,LIPO,FLO,AFA,ALEA,WEIGHT
0125       15 FORMAT(1H0,2I3,F8.2,F8.3,3F8.2,2F8.2,F8.2)
0126          GO TO 2

      C FEEDING REPORTS (FIVE MINUTELY INTERVALS)

0127       16 IF(FLOAT(MINUTE)/5.0-FLOAT(MINUTE/5).GT.PERIOD/5.0) GO TO 2
0128          WRITE(6,17)HOUR,MINUTE,METABR,ACON,ABSOR,LIPO,FLO,AFA,ALEA,WEIGHT
0129       17 FORMAT(1H ,2I3,F8.2,F8.3,3F8.2,2F8.2,F8.2)
0130          GO TO 2

      C END OF WORKING PROGRAM
0131          END
```

Fig. 6. Time adjustments and reports of current values of variables.

real time clock (statements 101–111). Thus statement 101 increases the clock seconds (SECOND) by the calculation cycle duration (CYCLE sec, statement 38). When SECOND reaches 60, statement 102 no longer causes the program to skip over statement 103 and 104 which increase clock minutes (MINUTE) by one and reset SECOND to zero. Similarly, when MINUTE reaches 60 (statement 105–107) and the number of calculation cycles (N) reaches the number for 24h (statements 108–111), they are reset to zero and the clock hours and the clock days are advanced accordingly.

When the specified number of days (statement 36, Fig. 2) has been run, the program stops (statement 119).

2. *Daily Reports*

Each time a new day starts (i.e. statement 111 has been reached), statements 113 (Fig. 6) onwards are reached. The last day's increases in fat energy (statement 113) and non-fat energy (statement 114) are calculated and reported with the day number in typed output (statements 115 and 116). The fat and non-fat energy tags are reset to current energy values (statements 117 and 118) for the coming day's increments.

If another day is to run, titles for a new page of data columns are printed (statements 120 and 121).

3. *Other Output Routines*

The program puts out regular reports of the current values of key variables. If no feeding tendency exists, statement 122 (Fig. 6) permits statement 123 to be read, which permits statements 124–126 to put out a report of the current time, metabolic rate (kcal/min), stomach contents (Mcal), absorption, lipoflow, and net non-fat energy flow rates (kcal/min), fat and non-fat energy (Mcal) and body weight (kg) when the clock minutes have been reset to zero by statement 107, i.e. on the hour every hour between meals. Because flow values change much faster during meals, the program is constructed to report every 5 min (statement 127) while feeding is going on (statement 122). Other parts of the program bound these meal reports with output at the start (statement 85) and finish (statement 93) of the meal.

D. *Output From a Sample Run*

Matrix printer output from this program is given in part in Fig. 7.

The first line of values in the output precedes the first calculation cycle, but the second line reports the values calculated for 1 a.m., at basal metabolic rate with the gut empty. As was seen on later days of simulation and is often the case in reality, the stomach is empty by the small hours of the morning. LIPO was negative, i.e. there was lipolysis. FLO was also negative, i.e. there was utilization

```
 TIME     METABR     GUT     ABSOR    LIPO      FLO      FAT      LEAN     WEIGHT

  0  0     0.00    0.000     0.00     0.00     0.00     0.00     0.00     75.00

  1  0     1.25    0.000     0.00    -0.62    -0.63    86.59   191.21     74.98

  2  0     1.25    0.000     0.00    -0.62    -0.63    86.55   191.18     74.97

  3  0     1.25    0.000     0.00    -0.62    -0.63    86.51   191.14     74.95

  4  0     1.25    0.000     0.00    -0.62    -0.63    86.47   191.10     74.93

  5  0     1.25    0.000     0.00    -0.62    -0.63    86.44   191.06     74.91

  6  0     1.25    0.000     0.00    -0.62    -0.63    86.40   191.02     74.90

  7  0     1.25    0.000     0.00    -0.62    -0.62    86.36   190.99     74.88

  8  0     1.71    0.000     0.00    -0.82    -0.89    86.32   190.95     74.86

MEAL STARTED   TIME  8 20    MEAL-MEAL INTERVAL  500   MINUTES
  8 25     2.10    0.206     0.00    -0.99    -1.11    86.30   190.92     74.85
  8 30     2.30    0.427     2.45    -0.00     0.15    86.30   190.92     74.85
  8 35     2.45    0.642     3.78     0.66     0.67    86.30   190.92     74.85
  8 40     2.57    0.854     4.73     1.12     1.03    86.30   190.93     74.85
MEAL STOPPED     TIME  8 40     MEAL SIZE    512  GRAMS    OFF USED 1.08

  9  0     2.92    0.789     5.53     1.37     1.23    86.33   190.95     74.86


MEAL STARTED     TIME 19 10     MEAL-MEAL INTERVAL  325   MINUTES
 19 15     2.17    0.206     0.07    -0.99    -1.11    86.44   191.06     74.91
 19 20     2.27    0.427     2.45     0.02     0.17    86.44   191.06     74.91
 19 25     2.32    0.642     3.78     0.73     0.73    86.44   191.06     74.91
MEAL STOPPED     TIME 19 29     MEAL SIZE    475  GRAMS    OFF USED 1.10

 20  0     2.26    0.671     5.11     1.51     1.34    86.49   191.11     74.94

 21  0     1.99    0.405     3.99     1.04     0.97    86.57   191.18     74.97

 22  0     1.72    0.205     2.87     0.56     0.60    86.62   191.23     74.99

 23  0     1.45    0.072     1.76     0.09     0.22    86.64   191.25     75.00

           END OF DAY  1    FAT    2.5    LEAN    1.4


MEAL STARTED     TIME 18 59     MEAL-MEAL INTERVAL  320   MINUTES
 19  0     2.23    0.000     0.19    -0.96    -1.07    86.45   191.07     74.92
 19  5     2.20    0.229     0.10    -0.99    -1.11    86.44   191.07     74.91
 19 10     2.31    0.449     2.62     0.08     0.22    86.44   191.06     74.91
 19 15     2.36    0.664     3.88     0.77     0.76    86.44   191.07     74.92
MEAL STOPPED     TIME 19 19     MEAL SIZE    487  GRAMS    OFF USED 1.11

 20  0     2.25    0.640     5.00     1.45     1.29    86.51   191.13     74.94

 21  0     1.98    0.381     3.88     0.97     0.92    86.58   191.19     74.98

 22  0     1.71    0.188     2.76     0.50     0.55    86.63   191.24     75.00

 23  0     1.44    0.063     1.64     0.02     0.17    86.64   191.26     75.01

           END OF DAY  3    FAT   -3.9    LEAN   -2.6
```

Fig. 7. Output from the basic model as programmed in Figs 1–6, showing the start and finish of the first simulated day and the finish of the third day.

of liver glycogen and/or muscle amino acids and other non-fat energy sources. While metabolic rate was at its resting value (1·25 kcal/min), this energy flow to the non-fat compartment was not deficient enough to trigger feeding. However,

the 0800 report shows that, as waking activity increased on a still empty stomach (GUT = 0), FLO fell deeper into deficiency. When FLO reached the hunger threshold, feeding began at 0820, 500 min from the start of the simulation).

Nothing metabolic improved for the first few minutes of the meal (0825 report). After the delay period for digestion, however, a little absorption began and net energy flow began to be ameliorated. In this program, the activity level somewhat unrealistically continued to rise during the meal, on its ramp from sleeping to working. The thermic effect of food also contributed to this rise in METABR. Despite that, the deficit of absorption (ABSOR) relative to metabolism was eliminated and lipolysis ceased, some of the increasing excess energy then being diverted into fat synthesis (LIPO becomes positive by 0830). When the cumulative food intake 6 min previously was great enough to provide absorption sufficient to bring non-fat energy flow to the satiety threshold, the meal stopped after a not unrealistic 20 min and moderately hearty 512 g. The initial value given to the satiety threshold was close to the value the simulation would acquire when it settled down, and so this first breakfast was similar to that on later days of simulation.

The next segment of output in Fig. 7 shows the simulated first evening meal and the first 24-h increments in fat and lean energy (kcal). The final segment is the last lines of this simulation, giving the third day's supper and energy increments.

Figure 8 gives the complete output from the second day of this simulation. The metabolic parameters up to the end of breakfast were identical to those on day 1. However, supper on day 1 had conditioned satiety to a slightly lower threshold and so the meal was a little smaller. As breakfast was passed from the stomach, so absorption showed, and—helped somewhat by the energy expenditure at a full working level (METABR = 2·7)—the net energy flow became low enough to trigger the start of lunch at 1317. In this highly determinate system, always eating the same menu, all meals are of fairly similar size.

Rather less had to remain in the stomach for supper to be triggered at 1904, because work had ended and activity was on its slow downward ramp through the evening, creating less energy loss.

Some food was still left in the stomach at bedtime, 2330, and so net energy flow to the non-fat compartment (FLO) was not even slightly negative. Once the system was simulating sleep, energy flow became substantially negative when the stomach had emptied, as has been seen from the early morning hours in both Figs 7 and 8. Yet the sleeping metabolic rate was low enough not to create an energy flow shortfall severe enough to reach the usual hunger threshold. So the empty stomach does not under these conditions trigger a midnight binge. Subjects with a lower effective hunger threshold or with higher activity levels when they should be asleep would be predicted to behave differently: such may

```
 TIME     METABR     GUT     ABSOR    LIPO      FLO      FAT     LEAN    WEIGHT
  0  0     1.28    0.007     0.63    -0.37    -0.28    86.63   191.25   75.00

  1  0     1.25    0.000     0.00    -0.62    -0.63    86.59   191.22   74.99

  2  0     1.25    0.000     0.00    -0.62    -0.63    86.56   191.18   74.97

  3  0     1.25    0.000     0.00    -0.62    -0.63    86.52   191.14   74.95

  4  0     1.25    0.000     0.00    -0.62    -0.63    86.48   191.11   74.93

  5  0     1.25    0.000     0.00    -0.62    -0.63    86.44   191.07   74.92

  6  0     1.25    0.000     0.00    -0.62    -0.63    86.41   191.03   74.90

  7  0     1.25    0.000     0.00    -0.62    -0.63    86.37   190.99   74.88

  8  0     1.71    0.000     0.00    -0.82    -0.89    86.33   190.95   74.86

MEAL STARTED     TIME  8 20     MEAL-MEAL INTERVAL  771    MINUTES
  8 25     2.10    0.206     0.00    -0.99    -1.11    86.31   190.93   74.85
  8 30     2.30    0.427     2.45    -0.00     0.15    86.30   190.93   74.85
  8 35     2.45    0.642     3.78     0.66     0.67    86.31   190.93   74.85
  8 40     2.57    0.854     4.73     1.12     1.03    86.31   190.93   74.85
MEAL STOPPED     TIME  8 40     MEAL SIZE   500  GRAMS    OFF USED 1.06

  9  0     2.92    0.767     5.46     1.33     1.20    86.34   190.96   74.87

 10  0     2.87    0.479     4.34     0.74     0.73    86.40   191.02   74.89

 11  0     2.81    0.259     3.22     0.14     0.27    86.43   191.05   74.91

 12  0     2.75    0.106     2.10    -0.37    -0.29    86.42   191.05   74.91

 13  0     2.70    0.020     0.98    -0.83    -0.89    86.38   191.01   74.89

MEAL STARTED     TIME 13 17     MEAL-MEAL INTERVAL  277    MINUTES
 13 20     2.68    0.123     0.60    -0.98    -1.10    86.37   190.99   74.88
 13 25     2.73    0.346     1.70    -0.53    -0.50    86.36   190.99   74.88
 13 30     2.82    0.564     3.36     0.22     0.32    86.36   190.99   74.88
 13 35     2.87    0.776     4.40     0.77     0.76    86.36   190.99   74.88
 13 40     2.91    0.985     5.23     1.21     1.11    86.37   190.99   74.88
MEAL STOPPED     TIME 13 40     MEAL SIZE   575  GRAMS    OFF USED 1.12

 14  0     2.94    0.890     5.87     1.55     1.37    86.40   191.02   74.89

 15  0     2.89    0.578     4.75     0.96     0.91    86.47   191.09   74.93

 16  0     2.83    0.333     3.63     0.36     0.44    86.51   191.13   74.95

 17  0     2.77    0.155     2.51    -0.20    -0.06    86.52   191.14   74.95

 18  0     2.50    0.044     1.39    -0.56    -0.55    86.50   191.12   74.94

 19  0     2.23    0.001     0.27    -0.93    -1.03    86.45   191.08   74.92

MEAL STARTED     TIME 19  4     MEAL-MEAL INTERVAL  324    MINUTES
 19  5     2.21    0.000     0.17    -0.96    -1.07    86.45   191.07   74.92
 19 10     2.19    0.229     0.08    -0.99    -1.12    86.44   191.07   74.91
 19 15     2.29    0.449     2.62     0.09     0.23    86.44   191.06   74.91
 19 20     2.34    0.664     3.88     0.78     0.77    86.44   191.07   74.91
MEAL STOPPED     TIME 19 24     MEAL SIZE   487  GRAMS    OFF USED 1.10

 20  0     2.26    0.665     5.09     1.50     1.33    86.50   191.12   74.94

 21  0     1.99    0.400     3.97     1.02     0.96    86.58   191.19   74.97

 22  0     1.72    0.201     2.85     0.55     0.59    86.63   191.24   75.00

 23  0     1.44    0.070     1.73     0.07     0.21    86.64   191.26   75.01

          END OF DAY  2   FAT   7.1   LEAN   7.1
```

Fig. 8. The complete second day from the simulation programmed by Figs 1–6.

be some of the causes of unusual amounts of feeding late at night. As the time during sleep at which the stomach empties does not affect the timing or size of breakfast, late night binges would not be compensated in the short term and the system could rely only on long term feedback to avoid gaining weight. Conversely, too little activity by the time food was presented after waking would leave the system above hunger threshold—possibly one reason why some people can only take coffee at breakfast.

The pattern of gastric contents and metabolic flow rates around the clock on day 2 is given in Fig. 9.

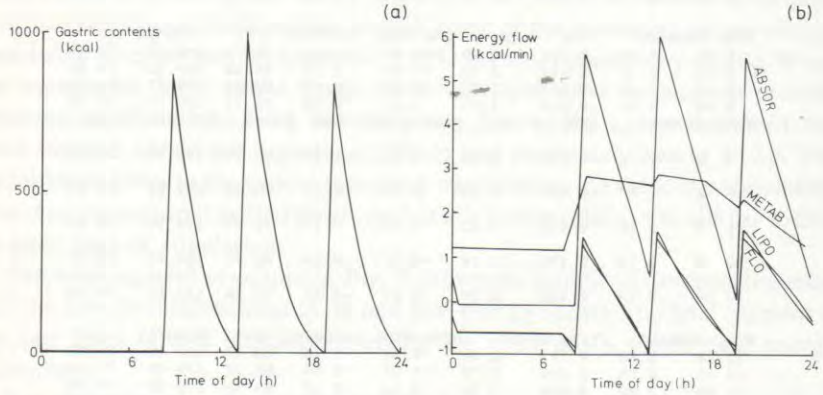

Fig. 9. Output from the basic model, reprogrammed to record the values of variables at every calculation cycle of day 2 and to plot them graphically: a, gastric contents (kcal); b, rates of absorption, total metabolism (heat output), lipogenesis–lipolysis and flow into or out of the non-fat compartments (kcal/min).

III. Programming and Computer Use

The program given in the previous section is written in the language Extended Fortran IV as used on an ICL 1906A computer. Fortran is a versatile scientific programming language to which computer operating systems on both departmental and university computers here are well adapted and in which model optimizing and testing routines are readily available.

This and other versions of the present model have also been written in the language Basic. Both that language itself and the systems available to us for operating with it are particularly suitable for introductory teaching purposes. Most of the program statements read naturally even to those not familiar with Basic or any other programming language. A program in Basic can even be edited in a number of ways by someone who is not fluent in constructing programs. We find it convenient to use time-shared systems in Basic, on a

departmental computer when only a few terminals are needed as in the tutorial situation, and on an inter-university system when each student in a class is using a terminal. However, a relatively high-level and simple language like Basic is at present available only at an appreciable cost in flexibility and computing speed. On a small computer like our department's PDP-11, the few days of real life that might take a night's run to simulate in Basic take only a few minutes in Fortran. When the computer is not being used over the weekend for other work, 15 years of a human lifetime can be simulated using a Fortran program.

Languages like Basic and Fortran can be learned very quickly—almost painlessly if one works with an already operative program which has a familiar scientific basis. Someone using a model like the present one for a while should be able to modify it radically to his own needs, or might even throw it away and build his own model. Short programming courses are widely available, however, and it can be better to take one: they provide a systematic introduction into all aspects of use of a programming language, and the user is less likely to find himself lost at times in the manuals for the local language or operating system or to be a pest to his colleagues who are programming literate.

IV. Some Tests of Properties of the Model

A. *Adjustment Procedures*

Our approach to modelling is primarily empirical, in the sense that each component function and parameter value in the model could in principle be derived from independent experimental data. However, at present there are some components in the human model for which quantitative data are almost totally lacking. Furthermore, there seems likely to remain for some time a considerable latitude within which parameter values and even function characteristics for most components could be varied and remain consistent with data. In this situation, we should seek the numbers that work best, within the ranges that data permit.

1. *Optimization*

If some criterion can be specified for the overall performance of a version of the model, the values of major parameters can be adjusted to meet this criterion. We have used an optimizing routine from the Nottingham University Algorithm Library (No. EO4CCF). This minimizes a general function of the required number of independent variables, using a Simplex method (Nelder and Mead, 1965). The reiterative calculations adjust the variables—the parameter values chosen from the model for optimization—to meet the criterion of optimum performance, for example a minimum change in body weight over a given number of days.

2. *Sensitivity Testing*

Even if the elements of the model were entirely determined by empirical data, and not in part by optimizing considerations, it would still be instructive to see the effects on the model's output when the values of some parameters were varied. The results provide an analysis which can indicate which parts of the model are most critical to the output generated, whether the "predictions" put out be realistic or not. That is, merely computational "experiments" can elucidate the sensitivity of the model to variations in its different components.

3. *Adaptation*

The basic model presented here has a limitation which would be expected to narrow the range of useful sensitivity tests to small deviations from the optimized (or experimentally precisely determined) values of variables and to short term effects of such deviations. None of the functions in the model *adapts*. That is not to say that the basic model as a whole fails to show adaptive responses to disturbance or that its undisturbed operation is maladaptive in some way. It is to say that there is not a *parameter* in any function whose value is dependent on the value of the output variables from another function. Functions are not interdependent or dependent on changes in external conditions, even though the values of *variables* calculated according to the various functions are of course highly dependent on the values of variables input from other functions. For example, the level of the metabolic rate variable influences the level of the momentary rate of gastric emptying, another *variable,* by affecting the timing of meals and hence the contents of the stomach. However, a persisting high level of metabolism (e.g. because of hard work or a cold environment) does not in the basic model adapt the gastric emptying rate constant, which is the main *parameter* in that gastric clearance function. This non-adapting gastric emptying rate constant is almost certainly unrealistic. Changes in eating rate may also adapt the gastric emptying rate constant. Persistently high absorption rates may adapt the proportionality factors (which reflect hormone secretory responses) controlling fat synthesis or mobilization. And so on around the model. Quantitative experimental determinations of the adaptive relations between persisting values of variables and values of functions' parameters will obviously be important in the development of a model to give realistic output in simulations of long term effects.

One qualification must be entered on the above: one function in the basic model does adapt, in the sense that all learning is adaptive—the conditioned satiety function. In this case, the maximum postprandial value of the FLO variable resets the value of the parameter which determines at what FLO value the next meal will be ended. It remains to be seen whether conditioning, i.e. adaptation of interneuronal relations, is important in any of the physiological adaptations mentioned above. It is generally expected that such adaptations will

be systemic (e.g. in the pancreatic or intestinal cell) but recent evidence that anticipatory responses of pancreas (Woods and Porte, 1974) and intestine wall (Saito *et al.*, 1976) are neurally mediated may serve to warn that this presupposition should be modified.

B. *Optimization for Constant Body Composition*

Most mature adults change in body composition very slowly compared with the rate of flow of energy through the body, and for that matter compared with the variations in composition of the diet and intensity or quality of motor activity. The basic model contained one simple function specifically designed to achieve long term stability (statement 70). Nevertheless, it seemed sensible at this stage to exclude from the model any powerful short term influence tending to change body composition.

We therefore chose six key parameters whose values were to be adjusted to minimize changes in the fat and non-fat energy of the body over several days of simulated processing (Section IV.A.1). These parameters were the rate constants for gastric emptying (STOMAK), lipogenesis (INFAT), lipolysis (OUTFAT) and lipolytic feedback from fat store (FATFBK), the hunger threshold (MINFLO) and the target satiety level (MAXFLO). The body stability criteria were changes less than 0·33 kcal in lean energy and 1 kcal in fat energy totalled over 7 days. When the optimization procedure had gone through sufficient iterations to produce no further change, values of about 0·19, 0·55, 0·4, 0·2, 1·5 and −1·1, respectively, were obtained. At the values given in Fig. 2, as can be seen in Figs 7 and 8 the simulation gained on average over several days no more than about 1 kcal/day of either fat or non-fat energy. This would amount to about 5 lb (2·3 kg) in 20 years, less than the population average rate of weight increase around middle age (Garrow, 1974). These optimized parameter values were in fact close to those we had originally chosen by scaling the rat up to human size. In an earlier version of this human model, without feedback from fat stores, the optimum values were also similar. That is, short term control by itself could be tuned to give a long term average effect of constancy in body composition while the conditions specified for that optimization were not disturbed.

The optimizations were run by varying the parameters of a given set of functions while leaving one particular constant set of values assigned to other parameters. The effect of varying these latter functions and values remains to be investigated. In particular, the activity pattern and metabolic rates were those used in the example of Section II.A.2.b—sleeping from 2300 to 0730, and working at 1·5 kcal/min between 0900 and 1700. Also assumed were a dietary energy density of 1·9 kcal/g, an eating rate of 25 g/min and a digestion lag of 6 min. With other values of these parameters, different values of the optimized

parameters would no doubt be required to keep body composition constant. Such calculations might therefore provide some basis for suggestions as to the types of adaptation of parameter value which might be used in the real person to help to preserve constant body composition. This would be an example of simulation work *generating* theory.

C. *Sensitivity of Body Constancy-Optimized Model*

To test how critical a parameter was to the food intake and body composition predictions of this example of the model, optimized and other parameter values were varied by at least 10% and in some cases by much more. The effects calculated on the timings and sizes of meals and on gain in fat and non-fat energy were averaged over a simulated 4 days, which followed 4 days from the start of run to ensure the simulation had had time to adapt fully to the conditions specified. A model without feedback from fat was used.

1. *Gastric Emptying Rate Constant*

As to be expected, the model was quite sensitive to modest variations in the characteristics of gastric clearance. These are represented by the rate constant and the exponent in the equation which is used to calculate current emptying rate from current gastric energy content (statement 55, Fig. 4). In this simplified

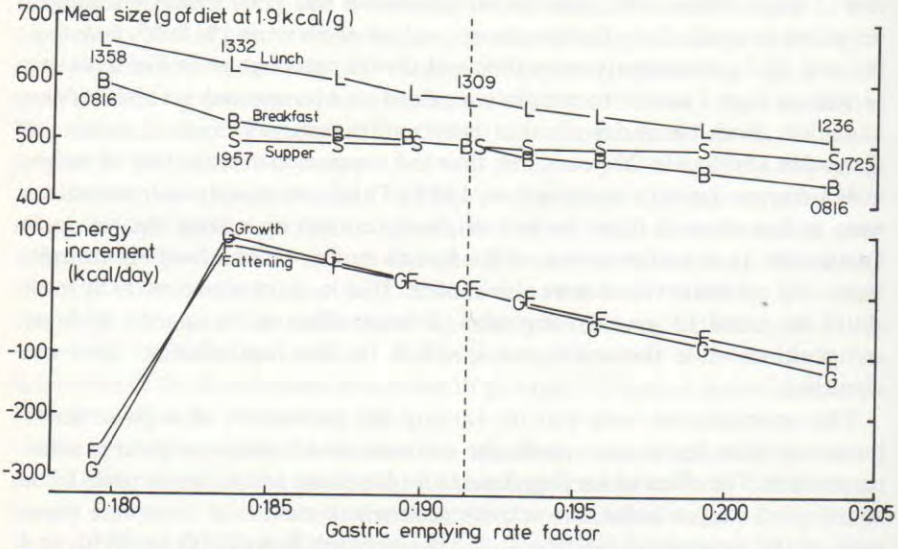

Fig. 10. Variation of gastric emptying rate factor around an optimized value of 0·1915. Average meal sizes and 24-h clock timings are given for the first (B), the second (L) and (when it occurs) the third (S) meal of the day and for the 24-h gain (or loss) of energy in fat (F) or non-fat (G) components of the parenteral mass.

model, the rate constant (STOMAK) would have to be adjusted according to the energy density of the diet if the simulation was to allow for the observed variations in emptying rate with energy density of stomach contents (Hunt and Stubbs, 1975). Faster emptying after ingestion of more concentrated diet may account for a correlation between chubbiness and energy density of the diet (Hunt *et al.*, 1975). Trowell (1975) has summarized evidence that lack of dietary fibre, not concentration of the diet, is a major cause of obesity because it makes for more efficient absorption. Booth (1976) argued that individual's gastric emptying characteristics as such, independently of energy density or fibre content, could be an additional factor in the varying propensities different people have to remain lean or to tend to obesity.

Meals decreased in size with faster rate factors and increased in size with slower rate factors, particularly at breakfast and lunch (Fig. 10). This is because the strength of satiety in the model ultimately depends on the relation between amount in the stomach and rate of gastric emptying: the less needed to get fast absorption, the smaller is the satiating amount of food. Larger meals are not rapidly compensated by smaller meals on other days (even with the long term feedback of the model of Section II), because the total amount eaten in a day (within wide limits) only determines when during sleep the stomach becomes empty and absorption stops—this having no behavioural effect. Therefore, larger meals generate net energy deposition and smaller meals permit net energy loss (Fig. 10). Breakfast stayed at 0816 and lunch stayed around the lunch hour, but supper became so late with the slower stomach that at a rate factor of 0·18 it dropped out altogether. This of course overwhelmed the energy depositing effect of the larger breakfasts and lunches which occurred with the slower stomach, and energy was lost rapidly (Fig. 10).

The direction of this effect is the opposite of that seen in the rat model, in which a fast stomach fattens (Chapter 11). The size and direction of the effect may be quite sensitive to the values of lipoflow parameters, particularly the point of changeover between lipolysis and lipogenesis and hence the stage towards the end of the meal at which the changeover occurs and affects meal size. More rapid emptying might falter if inoperative during meals or if ineffective at conditioning satiety.

2. *Lipoflow Parameter Values*

(a) *Changes in one value at a time.* Small variations in the factors in the equations which determine the proportion of spare energy deposited as fat (INFAT) or the proportion of energy shortfall covered by fat mobilization (OUTFAT) had effects on body composition which would be very substantial when cumulated over the long term (Fig. 11a,b). The effects on the meal pattern were minute, and yet of course a systematic small increase (or decrease) in meal size and slight consequential changes in meal timing occurred which were the

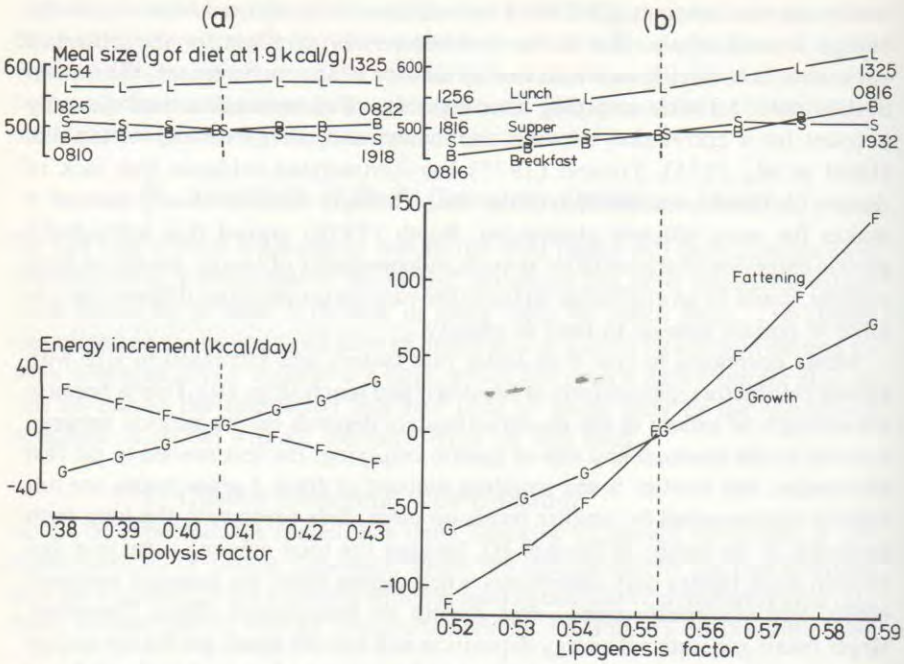

Fig. 11. Variation of lipoflow proportionality factors: a, lipoflow; b, lipogenesis. Symbols as in Fig. 10.

input on which the net body energy gain (or loss) was based. This is the all too familiar truism of weight control thermodynamics: a persistent minute "error" in meal size and total food intake will cumulate dramatically over the months and years. There is naturally an increase in delay to the next meal while a slightly larger meal is absorbed. Yet this does not compensate for the increase in meal size in the human subjects as modelled. The reason is the same as in the case of changes in gastric emptying characteristics—the behavioural irrelevance of the time the gut becomes empty during sleep means that (at least in the short term) one day's intake is disconnected from the next. In reality, people may have some mechanism to help the size of breakfast reflect, say, the time since the gut became empty: yet such a mechanism would have to be implausibly powerful to provide immediately the appropriate degree of full compensation. Thus the modelling encourages us to diagnose our long period of sleep as one of the weaknesses in the human feeding control system considered as a stabilizer of energy balance.

(b) *An elementary account of growth and obesity.* The pattern of effects on body composition of changes in the proportionality factors for lipogenesis and lipolysis suggests a summary analysis of mechanisms which could contribute to

normal growth and to the development of obesity. These suggestions also bring out how the lipoflow proportionality factors INFAT and OUTFAT could have physiological and biochemical meaning as parameters which lump together the effects of hormonal control of substrate distribution to tissues.

Table I.
Approximate body composition effects of varying the proportionality factors in the lipogenesis and lipolysis equations, in which lipoflow is set to be proportional to the differences between absorption and utilization rates

Lipoflow	Change in proportionality factors	Long term energy increment (arbitrary units) Non-fat	Fat mass	Total mass
1. Lipolysis	Decrease	-1	$+1$	0
2. Lipolysis	Increase	$+1$	-1	0
3. Lipogenesis	Decrease	$-\frac{1}{2}$	-1	$-1\frac{1}{2}$
4. Lipogenesis	Increase	$+\frac{1}{2}$	$+1$	$+1\frac{1}{2}$
Lipogenesis	Increase	$+1\frac{1}{2}$	0	"Pure growth"
Lipolysis	Increase			
Lipogenesis	Increase	0	$+1\frac{1}{2}$	"Pure fattening"
Lipolysis	Decrease ($\frac{1}{2}$)			

Table I summarizes the effects of variations in lipoflow factors such as those graphed in Fig. 11. In the range tested, increases and decreases in the lipolysis factor (OUTFAT) have relatively negligible effects on total body energy content. However, this is because the changes have complementary effects on fat and non-fat components, or—to use more conventional categories, introducing only slight inaccuracy— on adipose and lean body masses. That is, a reduced lipolysis factor fattens at the cost of wasting (loss of lean mass), and an increased lipolysis factor slims but increases lean mass, i.e. causes a form of "growth". On the other hand, changes in the lipogenesis factor (INFAT) do produce changes in total body energy content, according to the model. Reduced lipogenesis has a slimming effect but it also has a wasting effect, although the wasting is less in energy value than the slimming. Increased lipogenesis fattens but also to a lesser extent generates growth.

In reality, action of a hormone or some other control mechanism may be best represented by coordinate changes in both lipoflow factors. Insulin, for example, independently both augments lipogenesis and inhibits lipolysis. Growth hormone and/or other anabolic hormones may not merely augment lipolysis but directly or indirectly increase the turnover of fat. Alternatively, the anabolic hormones could be largely lipolytic but endocrine controls introduce lipogenic tendencies alongside that lipolytic effect by augmenting both the anabolic secretions and the secretion of insulin. In either case, the anabolic controls may be critical to whether energy is put into growth or fattening.

Growth without fattening or slimming would be generated by conjoint increases in both lipogenesis and lipolysis factors: addition of lines 2 and 4 of Table I gives 1·5 increments of lean mass with no net change in adipose mass. This is a simulation of a classical view of the role of growth hormone, with a proviso that insulin sufficiency is also necessary. Indeed, insulin has a somatomedin-like role.

Fattening without growth or wasting would result if an increase in the lipogenesis factor were co-ordinate with a decrease in the lipolysis factor to around half the extent. Line 4 of Table I plus half of line 1 would give 1·5 increments of adipose mass with no net change in lean mass.

The implications of this simple analysis need exploring for the techniques of body weight control which involve dietary control and the modification of feeding behaviour. One suspects that according to the model there would be no problem about sustaining growth (as in an immature human being) so long as no economic or other social constraints prevent intake from being adequate in amount and balance, and so long as the normal childhood hormonal pattern is present. For obesity, in contrast, one has the intuition that the model would require relatively heroic reductions in total intake to conteract a markedly fattening hormonal pattern or cellular response abnormality. This pessimistic analysis seems all too realistic in the light of what we know about the aetiology and therapy of obesity in many cases. However, for this and the several other aetiologies of obesity which are possible within the model, the simulation technique may at least provide a way of calculating the minimum required heroics—that is, the changes in feeding pattern which would be least hard to maintain in the face of their physiological, cognitive and social conditions and consequences.

3. *Energy Thresholds*

(a) *Hunger Threshold* (*MINFLO*). The model's output was relatively insensitive to minor variations in the level of energy flow shortfall which was sufficient to trigger feeding (Fig. 12a).

(b) *Target Satiety Level* (*MAXFLO*). The effective satiety threshold is adjusted in the model by a learning mechanism which predicts which level of energy flow at the end of a meal should, following a meal, produce a maximum energy flow at the target satiety level (cf. statement 99, Fig. 5). Thus although the satiety threshold is not a set parameter, its value is strongly determined by the target for postprandial maximum satiety.

Not surprisingly, changes in satiety target had substantial effects on meal size (Fig. 12b). The lower the target the smaller are the meals, and the higher the larger. There follows the effect of meal size on energy storage which is familiar by now. The storage effects are similar in lean and adipose mass: a more detailed

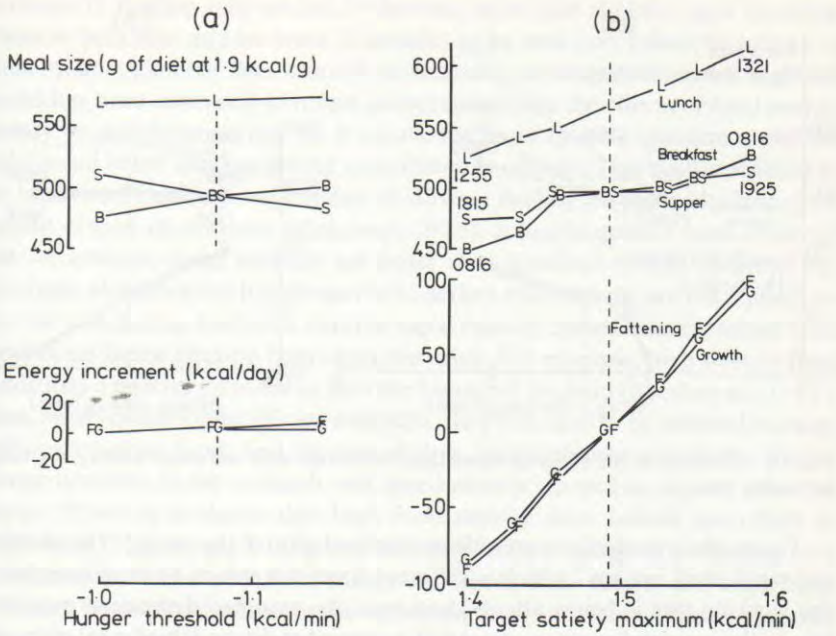

Fig. 12. Variation in meal onset and offset control parameters: a, hunger threshold; b, target satiety maximum.

model may be necessary to give an account of the differences between fattening and body-building effects of extra-hearty meals.

4. *Non-optimized Parameters*

(a) *Digestion delay.* The delay between gastric emptying and circulation of energy to the tissues proved not to be critical to performance of the model. This is partly because the learning mechanism for adjusting the satiety threshold is not programmed to show any effect of CS-US interval. It is also contingent on relatively linear characteristics of the increase in lipogenesis as absorption gathers pace.

(b) *Metabolic rate.* Substantial variations in the rate of energy expenditure during the simulated working day have considerable effects on feeding and body energy. It will be important to re-optimize parameter values for different basal and working metabolic rates. Indeed, adaptation of gastric clearance and lipoflow functions to metabolic rate would probably be realistic. Nevertheless, Fig. 13a shows simply the effects of variations in work output around the level of very light work which was used in these first simulations and in the optimization around which these sensitivity tests range.

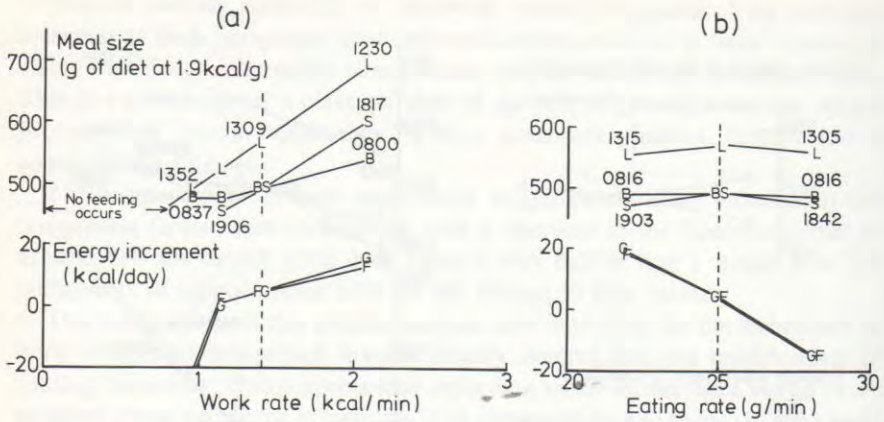

Fig. 13. a, Changes in rate of energy expenditure in external work and motor activity. b, Changes in feeding rate.

The model's predictions provide an interpretation of the saying "He who does not work shall not eat" which is different from that which St Paul intended. If the working rate is below about 1kcal/min, the assumed decreasing metabolic rate in the evening becomes so low that a somewhat delayed third meal of the day never begins. Indeed at 0·7kcal/min working rate, the hunger threshold is never reached at any time of day. These unrealistic predictions are partly contingent on having optimized the programmed parameters for a work rate of 1·4kcal/min. In particular, the hunger threshold may be too extreme. As discussed later, the concept of a simple threshold is highly questionable. Furthermore, even if it is used, a threshold should not be a determinate value as in this program, but should be subject to internal and external "noise" (as in the rat feeding model, Mark 3, Chapter 11). Eating would then tend to occur on occasion even at low work rate, in reaction either to an apparent slight shortfall in energy flow or to a high incentive feeding situation.

With increasing work rate, this optimization increases meal size and, despite the larger meals, starts feeding again earlier (Fig. 13a). At still higher energy expenditures, the simulations predict more than three meals a day. This may not be an unrealistic view of the situation where heavy work can be interrupted for refreshment breaks and food is readily available during such breaks. The simulation gains stored energy despite increased work, but the gain of non-fat energy is similar to that of fat energy, and so the cumulative effect would be "body-building", not increased adiposity.

(c) *Eating rate.* Reducing the feeding rate from the 25g/min on which the program was optimized caused slight variations in meal sizes with no clear trend, but a consistent tendency to put on lean and fat mass (Fig. 13b). Modest

increases in feeding rate tended to decrease meal size slightly, with resulting losses in both lean and fat mass. It remains to be seen how robust this result is when optimization has been carried out according to other criteria and when the model has been improved to reflect more realistically the effects of food energy density on gastric emptying. As it stands, the result raises a question about the widespread belief that fast eating contributes to obesity. This presupposition to the behaviour modification strategy of slowing feeding has been challenged on ground of lack of evidence (Mahoney, 1975). It has frequently been observed that on average obese subjects eat faster than standard weight subjects, but simplistic physiological hypotheses as to satiety mechanisms are not a justification for concluding forthwith that the rapid feeding causes obesity, rather than some other factor causing both characteristics. For example, high density food conditions a relative palatability into the flavour of the food (Booth *et al.*, 1972). Thus, when dense foodstuffs are available, they will tend to be selected increasingly over lighter foods and the rate of their ingestion may accelerate. Higher energy densities in the stomach will speed absorption and so deposit more fat energy. There is evidence that high food density does indeed contribute to chubbiness (Hunt *et al.*, 1975), but the many factors operative preclude a very strong correlation between food energy or carbohydrate density and eating rate.

It must be emphasized that at the very most these simulations raise a question about the conventional wisdom that slow eating slims. Without improved modelling and much more detailed analysis of model performance there would be no basis for suggesting that people *should* eat fast to slim. Nevertheless, insofar as the mechanisms modelled are an acceptable theory of satiation, the intuition that gobbling should fool the satiety mechanism is refuted by systems analysis computed within the indicated presuppositions.

V. Long-term Stability via Short Term Control

There has been considerable factual and conceptual confusion about so-called regulation of body weight. Mogenson and Calaresu analyse the problems in Chapter 1 of this book. In fact, in man there is no conclusive evidence that energy balance is kept constant on a day-to-day basis or even from one month to the next (Garrow, 1974). Furthermore, human body weight and adiposity do not on average stay strictly constant, but increase slowly even between 25 and 40 years of age. Nevertheless, the approximation to constancy from one year to the next is very close relative to the cumulative quantities of energy ingested as food and lost as external work, heat and excretion.

However, this degree of stability over the very long term does not in principle require a very precise feedback control mechanism of the type that an engineer would construct, in terms of which Brobeck (1965) defined the physiological concept of regulation and Hervey (1969) has discussed the specific problem of

the control of the amount of fat stored. There is a great variety of types of possible stabilizing influence, and many of them biologically more plausible than a thermostat-like control mechanism (Toates, 1975; Booth *et al.*, 1976a). As the point becomes more widely appreciated, so the uses of terms such as regulation, homeostasis and set point are qualified. They are offered as merely descriptive of the observed stability characteristics, allegedly losing their specific mechanistic implications. In contrast, our approach is to avoid the use of special words that tend to create unnecessary realities in the minds of their users or hearers. Rather we try to account for the observed degree and quality of stability by invoking known influences or by postulating biologically plausible mechanisms which are the simplest that can do the job.

A. *Control of Appetite and Satiety by Energy Flow*

However directly or indirectly the brain measures energy flow to non-fat tissues, as postulated in the theory behind the present model (Booth, 1972a,b), and by whatever combination of learned or direct effects the energy flows control feeding behaviour (Chapter 11, Section I.B.1), the short term control of timing and size of meals by their energetic interactions with utilization creates a powerful stability in the longer term. Providing that natural variation in the values of quantities in the system has a central tendency, variability in short term effects will tend to average out into a much less variable cumulative effect (Schilstra makes an analogous point in Chapter 9). The body may process relatively huge amounts of energy but it is a more or less fixed structure of viscera, bones, muscle and skin which carries out the processing. There are firm physical limits as well as narrower and subtler physiological limitations on what many body compartments can store or even process. Just a large tank filled from a tap and emptied from a drain will, within wide limits of inflow and outflow, find and roughly maintain a steady content for particular orders of inflow rate and drain diameter. The pond on the village green has no cistern mechanism.

B. *Basal Metabolic Rate*

The biochemistry of energy utilization adjusts to changes in conditions in a number of ways which tend to stabilize energy exchange and shift energy balance closer to the null point than it would otherwise be.

Heat loss increases with lean body mass. This is numerically a relatively tiny stabilizing effect. Nevertheless, the greater energy cost of maintaining more tissue is a limitation on tissue accretion.

Energy utilization becomes more efficient as a period of restricted intake lengthens. This effect normally asymptotes. Nevertheless, it limits the rate of tissue wastage under transient insult.

Some have suggested that overfeeding reduces the efficiency of energy utilization. This effect of "luxuskonsumption" has never been proven to physiologists' general satisfaction, but it may yet turn out that some people show such an effect under some circumstances (Garrow, 1978). This could be a more substantial limit on energy accumulation.

Basal metabolic rate and the energies of posture and movement are complex functions of adipose mass or adiposity (adipose as proportion of total). Some relations (e.g. the insulating properties of fat) are destabilizing. An effect of sense of effort on tendency to move would also be dysregulatory, and the inactivity of some obese people is well known. On the other hand, given (say) the maintenance of a certain speed of movement, the energy cost of distorting and carrying adipose tissue would be a restraining effect on its accumulation.

Probably none of these effects is particularly powerful, but they should be represented in a full model so far as each is evidenced.

It should be noted that there may be large individual differences in efficiency of energy utilization or in basal metabolic rate relative to body weight. These differences are not regulatory mechanisms for individuals but they should produce large individual differences in total intake and feeding pattern. Where social influences based on average intake or pattern hold sway over an individual who otherwise might be at an extreme of low (or high) intake, the low (or high) metabolic rate can be dysregulatory and fattening (or anorexigenic).

C. *Bias of Energy Flow by Size of Energy Store*

1. *The Feedback Mechanism*

One very simple form of negative feedback, which is to some extent already experimentally supported, could in principle be sufficiently powerful to provide a greater degree of stability of adiposity or body weight than is in fact observed in man. This is because, although at a given moment the feedback influence might be mixed with large short term variations, the feedback would be persistent at an average level which was monotonically related to the deviation of the amount of stored energy from a value which would be in equilibrium with fat-depositing tendencies and so would exert a strong long term control.

The general form of such a feedback would be a change in the energy store (i.e. a flow of energy into or out of it) which is proportional to some power function (exponent c) of the size (S) of the store:

$$\Delta S = kS^c$$

The store could be lean mass, in which case we are talking about a bias to growth or to wasting. More relevantly to the adult human case, the store could be adipose mass, and the bias be lipolytic or lipogenic (and both may exist simultaneously). In the arithmetically simple case where $c = 1$, lipolytic and

lipogenic functions can be added to give a single equation which may be net lipolytic or lipogenic. Positive exponents on wasting or lipolytic functions and negative exponents on growth or lipogenic functions provide negative feedback—that is, tend to stabilize body energy.

A background lipolysis in proportion to adipose energy content (or a background lipogenesis in inverse proportion) would severely restrain tendencies to put on fat and would help take it off in the absence of such tendencies. Such background could be local, depending on cell structure, or it could be distributed, for example in a phenomenon such as insulin resistance. In fact, basal lipolysis *in vitro* increases as human adipose cell size increases (Goldrick and McLoughlin, 1970). As it has turned out, the basic prototype model happens to operate in such a way that the direction of short term effects on fat storage depends largely on lipolysis or turnover rather than on modulation of absolute lipogenic flow (Section IV.C.2.b).

Until such time as experiments in man *in vivo* under normal conditions provide an estimate of basal lipolysis as a function of adipose energy, and this in turn is related to feeding behaviour, the properties of such a stabilizing mechanism will have to be explored merely by conceptual experiments. The basic prototype model of Section II includes a lipolytic feedback equation in the energy flow calculation. Its proportionality factor (and exponent) could be set at other values, the other parameter values optimized to give equilibrium adiposity in the normal range and then the sensitivity tested of these models to prefattening, preslimming and imposed fattening or slimming influences.

The long term stabilizing properties of the program of Section II have been preliminarily tested simply by altering the initial body fat content and running the simulation for many months. As expected, the feedback from fat stores does tend to return body weight, and particularly its fat component, to a value which is preferred under the other conditions of simulation (Fig. 14). However, with the FATFBK parameter value used, which is of an order compatible with data on basal lipolysis in human adipose cells *in vitro*, the loss of excess fat and the correction of fat deficit is interestingly slow—taking years to lose or gain 10 kg, not days or even months. If this is a realistic computation of the quantitative effect of this type of negative feedback in man, then it may prove beyond the power of existing data to discriminate between such an equilibrium theory of weight control and a theory of "buffered" levels of energy store (Garrow and Stalley, 1975). The body weight changes were achieved by relatively miniscule changes in food intake. Very small changes in lean mass occurred along with the large changes in adipose mass.

Garrow (1974) has argued that excursions in human energy balance can be so large and their corrections where they occur (whether in part or whole) are so delayed that the observed stability characteristics can be attributed to the individual's perception of his own weight or form and his deliberate control of

food intake and/or energy expenditure. Nevertheless, people differ greatly in the speed and extent of weight change and even a change in adiposity which is very large, relatively rapid and never fully corrected is not a phenomenon that is evidence against a simple physiological feedback from fat store to appetite. Such a feedback has to operate in the context of many other influences. If it is not the

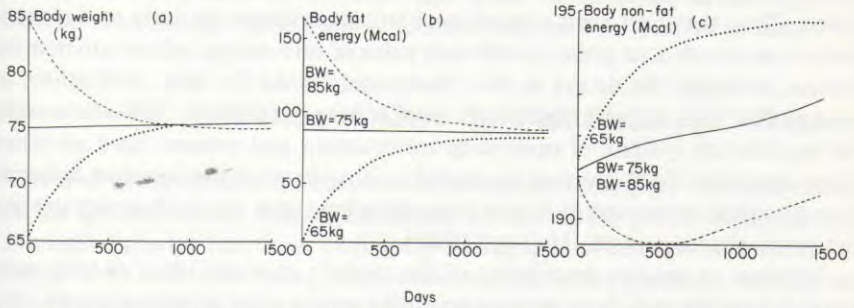

Fig. 14. Longterm stability of: a, body weight; b, fat energy; and c, non-fat energy in the basic model when the initial body composition is normal or is increased or decreased in adipose tissue content by 10 kg. Note that the scale for non-fat energy is 30 times more expanded than the scale for fat energy, and that the fat gain of the simulation starting at 75 kg, although also miniscule, is three times greater than the graphically more more obvious gain in non-fat energy over about four years.

type of feedback that involves assessment of deviation from some particular preset privileged value of fat store size, then the stable value of fat store will depend on other conditions in the system, or under some unfortunate circumstances there may be no permanently stable value towards which fat store size tends. As discussed in Section IV.A.3, a particularly important possibility is that components of the system adapt as the system is persistently operated under new conditions. Whatever feedback from fat store to appetite might exist could itself adapt to persistently high storage rate, turnover or amount—adaptation which is as likely in principle to attenuate the negative feedback effect as to strengthen it.

Thus, the fact that someone has grossly increased in weight and shows no sign of losing weight, or even appears to be continuing to get fatter indefinitely and has extreme difficulty in stopping weight increase at any level, is not evidence against the existence of the kind of feedback function proposed above. The evidence against it would be (the very difficult) measurement of the quantitative relation between adipose triglyceride content or cell size and long-term net mobilization and then the calculation of the effects of the operation of such a functional relation in a feeding control system with other defined characteristics. That is, systematic computation not only aids the formulation of experimental design. It is likely also to prove essential to definite interpretation of the results.

2. *Short Term Set Point and Long Term Equilibrium Point*

In the present model the energy flow rate to non-fat tissues at which feeding stops is about equal and opposite to the rate at which feeding starts. That is, the short term control system has a preferred value of energy flow (approximately zero), even though the flow is never more than transiently at that value because of the considerable inflow which builds up towards the end of a meal and the considerable utilization of non-fat energy which is occurring by the time a meal starts. Thus the short term control mechanism performs similarly to a closed-loop system with a set point or reference value of zero energy inflow into non-fat tissues, although the delays in this "energostat" make for large oscillations in energy flow rate. As just emphasized, a major long-term control could be merely an equilibrium system, of open loop construction and without fixed set point characteristics. To this extent the model is in contrast to the common assumption that short term control is open loop while long term control has very precise set point characteristics (Hervey, 1969).

Whether or not the description of the model's characteristics as long term equilibrium-like and short term set point-like proves to be broadly accurate, and whether or not this model is realistic to the observed phenomena, this point illustrates the potential value of any detailed analysis of a system. The general terms used to describe the system's behaviour often prove to be "chapter headings" for characteristics which are not attributable to any one discrete mechanism but are properties whose generation is distributed diffusely through a number of processes. The more abstract concepts of the present model (e.g. "energy flow") are themselves subject to such reduction in due course. This does not in any way imply that the abstract control characteristics of internal variables do not exist. However, it does imply that there is a limit to the usefulness of repeated demonstrations of those functional characteristics by experiments which do not also provide evidence as to the mechanisms by which they are achieved. It would be more profitable to elucidate the mechanisms of stabilization of body weight or energy flow than to refine in great detail the data on their set point- or equilibrium-like properties.

Also, current theories of obesity might be more realistic if they used equilibrium-type stabilization concepts. Accounts of the hyper-reactivity of moderately obese and some normal-weight individuals to highly salient (and presumably therefore usually external) stimuli, in terms of relative deprivation (Nisbett, 1972) and restraint (Herman and Mack, 1975), do not require a body weight or adipose weight set point. Any displacement of equilibrium between feeding and fat in the direction of less feeding than would otherwise occur will release a stronger tendency to feed which is monotonically related to distance of fat store size from equilibrium. Furthermore, to the extent that an energy flow deficiency has undifferentiated distress components (as well as components learned to be ameliorable by feeding), restrained subjects will be more reactive to

all strong stimuli (arousal or general drive) as well as to strong feeding-related stimuli (specific conditioned drive and incentive), as has been observed (Schachter and Rodin, 1974). Indeed, where the distinctive distresses of hunger and oversatiation have been poorly discriminated (Slochower, 1976) or bias against response to them introduced (Griggs and Stunkard, 1964), then this general hyperemotionality or externality will be stronger relative to specific feeding reactivity than in subjects with better detection or lower response criteria, even though these normal subjects may be less reactive to food.

VI. Additions to Give the Full Prototype Model

A number of elements in the basic model of human feeding are very easily filled out for greater realism. Examples include improving the gastric emptying and intestinal digestion functions, adding a plausible level of noise to the detection of energy flow level, calculating basal metabolic rate more precisely, varying the pattern of activity and work done around the clock, and imposing variations in the composition and availability of food or the speed and continuity of feeding within the meal. Our general policy is to change the program as better data about components of the model become available. The incorporation of human fluid intake control might also be attempted, along the lines described by Toates for the rat in Chapter 14.

A. *Metabolic Expectancies*

One elaboration has been given high priority. In the basic version of the prototype model (Section II), the only role for learning is adjustment of the effective satiety threshold to create a target maximum energy flow after the meal. If the model were augmented to allow for feeding under varying conditions or on a variety of foodstuffs, each sensory condition of intake should determine its own acquired satiety threshold.

Learning certainly has a greater role than this in human appetite. Eating rate varies from one foodstuff to another, and where there is choice some foodstuffs are selected while others are rejected. Some, possibly most, of these variations in acceptability during or before ingestion of a foodstuff are acquired reactions to the appearance or orosensory qualities of the food, established by conditioning (Booth, 1977a). That is, we react enthusiastically to some foods in part because we have had long experience of the increases in supply of energy-yielding substances or amino acids to tissues which resulted when these foods were ingested while the supply was low. We may be unenthusiastic about other foods when we are hungry because they have failed to repair such current deficiencies in supply.

It must be noted that such effects remain to be demonstrated in man by formal experimentation. It would then be necessary to assess their importance relative to unlearned preferences and aversions, and to the intake-stimulating effect of variety, which depends on sensory adaptation, habituation or some other foodstuff-specific mechanism (Booth, 1976). However, conditioning of preferences and aversion to normal foods in infancy has been seen in animals (Reisbick, 1973; Booth *et al.*, 1974; Hogan, 1975). Furthermore, there are indications of importance of conditioned acceptability in man, even in adulthood. For example, loss of craving for carbohydrate foods is reported following ileojejunal bypass in the early phase when carbohydrate absorption is disrupted (Bray *et al.*, 1976).

Although the existence of nutrient-conditioned appetites and aversions in normal human feeding remains to be established, conditioned satiation and desatiation have been demonstrated in man using starch loads in relation to normal meals (Booth *et al.*, 1976b).

Indeed, the same starch load procedure has also been used to show the influence on human food intake and attitudes to food which is possessed by various internal states generated following ingestion, probably by the absorption of carbohydrate energy at differing rates (Booth, 1977b). The difficulties of showing suppression of intake or hunger sensations following ingestion of energy-rich foodstuffs under some conditions (Wooley, 1976) may arise from the variations in dietary composition not altering the relevant energy flow stimulus sufficiently, relative to the strong conditioned sensory qualities of the familiar foodstuffs used and the likely broad generalization over internal stimuli. Now, the intake suppression which is seen most strongly at about 20–30 min after a concentrated starch load corresponds to a peak in glucose absorption rate (Booth *et al.*, 1976a) which would come a few minutes after the meals had ended in the conditioned satiety experiment of Booth *et al.* (1976b). Thus energy flow rate change is a good candidate as the unconditioned stimulus with the associative property of creating appetitive or aversive conditioned stimulus value (anticipatory motivational power) in the conjunction which is experienced late in a meal of a particular dessert foodstuff and modestly positive values of energy flow (or the sensed correlates thereof).

So we come to the view that satiety generally and conditioned satiety in particular is a state-dependent selective aversion or rejection, where the state is an internal stimulus which occurs towards the end of a meal. This incipient satiety state could be a metabolic one (such as a particular energy flow rate), in whatever way it is detectable to the brain. Hungry behaviour on this view is also a state-dependent preference or acceptance, conditioned or not. Indeed, because the changes resulting from ingestion of a food depend on when during a meal it was taken, the same rich diet can come to be preferred in the state of low energy flow rate at the start of a meal and rejected in the state of high energy flow at the

end of the meal (Booth, 1977a, b), while conversely a poor diet may be rejected during hunger and accepted during incipient satiety. (These suggestions are formulated in terms of respondent behaviour, but intake could in part be operant—the analysis is concerned with stimulus–stimulus association, not with the details of response organization.)

Another way of stating this view is to say that internal and external states relevant to feeding are used to interpret each other and to predict the consequences of such a conjunction of cues. Remembered contingencies amongst foodstuffs and body sensations dominate the attribution of appetite and its satisfaction to one's own current state and the attribution of current acceptability or unacceptability to the particular food or drink.

This analysis has been programmed for the case of energy flow states in the full version of the prototype human feeding model. [Amino acid flow rates are due to be programmed in a separate representation of protein appetite acquisition (Booth, 1974)]. Correction of a negative energy flow, following experience of a foodstuff during low energy flow, conditions a preference in future for that foodstuff in the presence of that low energy flow. Failure to correct a low energy conditions an aversion to the food in that low flow state. Excessive energy flow conditions an aversion to the foodstuff in the presence of high energy flow.

Such a program performs very similarly to the basic model, at least in the version tested so far. The state-dependent conditioned responding provides an account of the start and stop of feeding which eliminates the thresholds used in the simplified model. With a variety of foods available, feeding starts when the unconditioned and conditioned acceptability for any one of them in compound with current energy flow becomes positive. Feeding stops when there ceases to be any food-plus-energy-flow compound stimulus eliciting acceptability. An availability parameter can also be incorporated, to represent the extent to which food is not immediately present and ingestable.

B. *Biochemical Reduction*

The energy flows in this model are literal sets of fluxes of specifiable energy-yielding metabolites. So, given sufficient information, the energy flow variables can be reduced to the biochemical level of particular substrates moving between particular organs or tissue types in the body. At present we have the impression that the experimental literature is insufficiently complete to permit the construction of the biochemical systems analysis of the freely feeding ambulant human subject which would be needed to make a realistic reduction to explicitly biochemical physiology. Understandably, biochemical physiologists have to date concentrated on simplified preparations such as postabsorptive man and the effects of specified loads such as glucose administered intravenously or perhaps orally. Some reasonable guesses can be made as to the distribution and

remobilization of dietary carbon between normally spaced meals, but firm data would establish the superiority of the biochemical reduction over our current simplification in terms of flows of metabolizable energy into fat and non-fat compartments. The strategic time to resolve the specification of energy flows into their substrate components would probably be when one of the many blood glucose regulation models manages to cover the case of periprandial man. Then hopefully that model could be integrated with ours with very little trouble. One major snag could be that we would have had to have identified the locations and characteristics of the satiety-hunger (i.e. metabolic conditioner or reinforcer) "transducer" or "receptors" before the detailed biochemical processing could be grafted onto the cognitive processing. It would certainly be necessary to have these functions detailed quantitatively, as well as much other neuronal processing, before realistic neurophysiological modelling could be included.

VII. Value of the Model

A. *Potential Uses of Simulation in the Obesity Clinic*

1. *Diagnosis*

A systems analysis based on measurable components could in principle be used to identify and to characterize the variables which are critical to an individual's weight control problem. Many other analytical techniques, e.g. most current varieties of multivariate statistical analysis, are inapplicable because the system does not perform by linear combination of independent variables.

At the very least, acquaintance with a realistic simulation tends to expose inadequacies in the preconceptions behind some clinical experimentation. For example, our simulations often emphasize once again how small an abnormality in gut function or hormonal control of fat metabolism could be sufficient cause of gross obesity in the long term. It may be possible to calculate how much the precision or sensitivity of current physiological, biochemical or behavioural measurements must be increased before we have a chance of identifying such a defect in a patient or a group of patients.

Simulation may also be necessary to the resolution of questions of primary or secondary causation. It may to some extent weaken their cogency, or at least expose the poverty of their therapeutic implications. Without quantitative systems analysis, the experimental approach to identification of a primary factor is somehow to eliminate or at least hold constant all other factors. Such simple designs are not generally practicable, and often are in principle fallacious. In contrast, data obtained by measured alteration of variables within a normal range can be fed into a computer model to identify (given a specification of

current functional contexts within the rest of the system) which variations are more critical than others. The conclusions then may be relevant to questions of how to begin to move the system from its current (mal)functioning.

2. *Therapy*

Accurate calculation of the processing in a single individual would require much better founded functions in the model. It would also require greater precision than is often currently available in the techniques for estimating the parameter values in those functions for an individual. Thus diagnosis and therapy by literally individual simulation may be a long way off.

However, a reasonably realistic general model of the control of human feeding and body composition could provide qualitative and semi-quantitative analyses of obesity in various classes of internal and external circumstances. The effects of various combinations of treatments on different types of obesity would be calculable in advance in no other way. Simulations of types of therapy would never justify by themselves firm recommendations as to clinical practice. However, they may yield general suggestions which would be sufficiently soundly based to justify proper clinical trial, or to raise serious questions about current clinical procedures.

3. *Theory of Obesity*

What is the point of trying out such a crude model of obesity? It is the first which can be used to test the very rough quantitative plausibility of particular theories of the aetiology or therapy of obesity, against a background of quantifiable assumptions which are as reasonable as can be constructed from the available data. Any particular assumption within such simulations is open to criticism and can be replaced by a more realistic assumption as soon as the basis of the criticism can be made accurately quantitative or at least computably operational.

Similar points could be made for the model of growth suggested in Section IV.C.2.b but not detailed further here. Framing theory in the form of a quantitative systems analysis provides an additional tool to determine what might be worth looking for in an infant, child or adolescent to relate to clinical problems of body composition or feeding (whether or not distinctive to youth), or to ensure the general provision of conditions within the range for normal healthy growth.

B. *Modelling as an Aid to Scientific Understanding*

Computer simulation, especially of a realistic interdisciplinary and reductive sort, is expensive in effort, time and money. A verbal statement of the theoretical

analysis behind such a model, augmented with diagrams, might be sufficient to direct experimental investigation of various component processes of the human feeding system. So, is the expense of simulation worthwhile?

The answer depends on a judgment whether we have begun to understand anything about the processes underlying human appetite and body change. If we consider that we do have a few plausible facts, then we are faced with the problems of putting these facts together predictively. One major problem is that, however well judged the simplifying assumptions and approximations, a realistic analysis of the processes by which feeding behaviour and nutrient utilization are determined will inevitably have a considerable complexity. Pre-programmed mechanized calculation is the only way to cope beyond some degree of complexity. Other problems with realistic verbal theories of hunger mechanisms will be unnoticed looseness, hidden inconsistencies and unintended implications. The discipline of specifying the processing with sufficient precision and coherence to generate predictions mechanically, whether they fit the facts or not, brings out these deficiencies in the theorizing. Once the model is specified adequately, the labour and unreliability of human intuition or even human calculation are avoided—or, rather, they are transferred to the more appropriate task of managing the use of scientists' time and computer costs involved in testing and applying the theory as modelled.

One of the trick questions to ask a modeller is what his model has told us that we did not know before. The question is tricky because modelling is a species of theory construction and not a species of empirical observation, and so a model can never tell us the sort of thing an experimental result can, which is what an illogical questioner wants. We are content for the modelling to be judged by the empirical work it will guide. If we find the model enables us to state better the thinking which informs experimental design, that will be everybody's gain if the theorizing embodied in the model is as adequate as any alternatives.

What a theory can do as a theory is deal with some theoretical problems. There follow a couple of illustrations, both concerning relations between scientific disciplines or levels of reality in human feeding control, and both related to trick questions which we have posed ourselves as well as had posed of us by others.

Does the model show that metabolism affects feeding or merely that feeding affects metabolism? This is intended as a criticism of the analysis for being fallaciously circular. All the question achieves is a complaint against reality—that is, it exposes unrealistic preconceptions about behavioural and biological causation. In general physiology, in cognition and in behavioural neurology, the rule is re-entrant causal sequences, not one-way causation. A system description which (if necessarily only in outline) is complete in the sense of autonomously workable will not be able to describe what is going on without very often implying that one process affects another and also this other process affects the

former. The present model is specified in terms of physiological and psychological variables which are in principle measurable. It couples the behavioural and the biological levels of phenomena together in a (probabilistically) determinate system. If therefore we had a set of assumptions or data which specified all the behavioural functions and all the physiological functions but one, the model could be used to predict physiology from behaviour and physiology together, even though it was originally constructed to predict feeding patterns from physiological and behavioural elements.

Another trick question is whether human feeding is biologically or socially determined. Our thinking on this was clarified by early runs of the prototype model. It was a considerable shock to find that a model of biological processes and cognitive adjustments to them predicted three meals a day and none at night—a pattern we had believed to be maintained by social convention and socially acquired individual habit. On consideration, however, this result does not justify a shift from the view that when (and even how much) an individual eats on a particular occasion can be strongly determined by immediate social, perceptual and physical exigencies. What the result does suggest is that the social conventions as to meal timings, and the cuisines and economics determining meal composition, have adapted to the biological demands generated by the pattern of life of the type of people in the society in question. Three major meals a day may be the most appropriate pattern when physical work at modest levels continues through 6–8 hours of the day without long breaks, under conditions where food can be readily obtained although generally in non-work locations.

Nevertheless, precisely when and where and what we next eat is a decision within a multilevel system in which a person's body and his own information processing are only two segments among several. The model should be elaborated so that the food availability parameter in the meal onset equations is susceptible to external influences, as also the food acceptability should be opened to interaction with motivations unrelated to feeding. Decisions as to the individual's location, companions, scheduling of activities and other social and physical choices may have a structure which can be specified. Then our cognitive feeder can be socialized, as well as given other things to do with his time.

In conclusion then, we present a model in a basic form with elaborations, which amounts only to a prototype because it operates only at the levels of physiology and learning, and with simplified algorithms even at those levels. A fully operational model would include social-cognitive functions as limiting conditions on the effective availability of foods and the relation of hunger to actual acceptance of food. It would also have biochemical functions to complement and in some cases to replace the prototype's physiological functions.

The model could in principle also have a neural level. In this prototype, and even in a fully operational model, perceptual, associative, motivational and motor processing can all be represented as functions at the behavioural level with

no explicit reference to brain processing. Indeed, contrary to some current stories, the improvement in predictive power for the behaviour of the normal organism to be made from incorporating brain processing equations should be expected to be negligible. However, the effects of drugs or of course brain damage on feeding behaviour are unlikely to be predictable without neural process components in the model. Furthermore, if the nutrient content of normal meals directly affects brain metabolism and hence synaptic transmitter function as has recently been suggested, however unlikely that would seem *a priori*, then some aspects of neural processing may be directly implicated in the detection of the current flow rate of energy-yielding or other critical nutrients (Booth and Stribling, 1978).

The results of even this prototype model suggest that the underlying theory of the energy flow cycle, unlike prior theories of hunger, may contribute to appetite physiology in particular and to psychosomatics generally an elucidation that could at best compare with that provided by the tricarboxylic acid cycle concept of Krebs for the biochemistry of intermediary metabolism. Beginning to test the model has at least been fun.

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